SPECTRUM OF LIVER INVOLVEMENT IN AUTOIMMUNE DISEASE

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CERTIFICATE

This is to certify that this dissertation titled **'SPECTRUM OF LIVER INVOLVEMENT IN AUTOIMMUNE DISEASE'** is a bonafide original work of **Dr.AMIT.G.Y** in partial fulfillment of the requirement for MD (General Medicine) Branch - I examination of the Tamil Nadu Dr.MGR Medical University to be held in March 2008.

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ABBREVIATIONS

- AIH – Autoimmune Hepatitis
- ANCA – Anti Neutrophil Cytoplasmic antibody
- ASMA – Anti Smooth muscle antibody
- ANA – Anti Nuclear antibody
- AMA – Anti Mitochondrial antibody
- ARA – American Rheumatological association
- ALT – Alanine aminotransferase
- AST – Aspartate aminotransferase
- ALP – Alkaline phosphatase
- ESR – Erythrocyte sedimentation rate
- HBV – Hepatitis B virus
- HCV – Hepatitis C virus
- LFT – Liver function test
- NSAID – Non steroidal anti inflammatory drug
- PT – Prothrombin time
- SLE – systemic Lupus Erythematosus
- RA – Rheumatoid arthritis

- RF – Rheumatoid factor
- LKM – Liver kidney microsome
- SLA/ LP – Soluble liver protein/ Liver pancreas
- PBC – Primary Biliary Cirrhosis
- PSC – Primary Sclerosing Cholangitis

1. INTRODUCTION

Chronic liver disease is an important cause of morbidity and mortality in developing countries [1].Along with co-existing complications of portal hypertension, liver failure and hepatocellular carcinoma, it puts an enormous burden on limited health care resources.

Common causes of chronic liver disease in developing countries like India are Hepatitis B virus and Hepatitis C virus related chronic hepatitis, alcohol, drug induced liver disease and metabolic liver disease. Etiology of liver disease in women, especially younger women is more likely to be chronic viral hepatitis and autoimmune disease [2].

Screening of blood transfusion donors and aggressive vaccination strategies are bound to reduce the prevalence of post hepatitic liver disease. Hence it is important to recognize early, other potentially treatable causes like autoimmune liver disease.

2. REVIEW OF LITERATURE

HISTORY

The first observation of a link between arthritis and liver disease was reported by Still in 1897 [3] and Wishart in 1903 [4]. This was followed by many attempts at inducing jaundice to ameliorate joint symptoms [5].

Search for the 'active agent' in this response induced by jaundice culminated in hypotheses that corticosteroid hormone metabolism was deranged in these conditions. This was followed by first reports of dramatic response to corticosteroid therapy in rheumatoid arthritis [6].

Waldenstrom and Kunkel were the first to recognize a syndrome of chronic hepatitis in young women with extreme hypergammaglobulinemia. Liver function abnormalities in rheumatoid arthritis and other connective tissue disorders were well established and attributed to systemic nature of underlying disease process in a review by Movitt and Davies in 1953[7].Through the next few decades many case series of patients with subclinical and clinical liver dysfunction associated with autoimmune diseases were reported [8,9,10].

In the last 25 years, there has been clarification of terminology from lupoid hepatitis to chronic active hepatitis and then to autoimmune hepatitis. The explosion of information in fields of genetics and molecular biology has given way to new opportunities in understanding the genetic and molecular basis for autoimmune liver disease.

DEFINITIONS

- **Chronic hepatitis**: A series of liver disorders, of varying cause and severity, of chronic inflammatory reactions in the liver as shown by liver function abnormalities and histology, and continuing without improvement for at least six months [11].
- **Autoimmune hepatitis**: Unresolving inflammation of the liver of unknown cause characterized by presence of interface hepatitis, portal plasma cell infiltration, hypergammaglobulinemia and autoantibodies[12].
- **Primary Biliary Cirrhosis**: Chronic progressive cholestatic liver disease that predominately affects middle aged women and is characterized by chronic inflammation and fibrous obliteration of intrahepatic bile ductules [11].
- **Primary Sclerosing Cholangitis:** Chronic progressive disorder of unknown etiology characterized by inflammation, fibrosis and stricturing of medium to large intrahepatic and extrahepatic bile ducts [11].

Classification of chronic hepatitis

Previous attempts at classifying chronic hepatitis based on localization and extent of inflammation, as chronic lobular, persistent and active [13] have now been challenged by recent observers. With currently available information, classification of chronic hepatitis based on combination of clinical, serological and histological variables is appropriate. Chronic hepatitis is now classifies as:

- **Classification by cause:**

1. Chronic viral hepatitis: HBV, HCV, HDV, unknown viruses
2. Autoimmune hepatitis: types 1, 2 and 3
3. Drug associated hepatitis
4. Non alcoholic steatohepatitis
5. Wilson's disease / α_1 antitrypsin deficiency

- **Classification by grade**:

It is histological assessment of necroinflammatory activity calculated by using histological activity index (HAI) given by Knodell [14] and Ishak [15].This index is based on the presence and extent of the following on liver biopsy specimens:

1. Periportal necrosis

2. Intralobular necrosis

3. Portal Inflammation

- **Classification by stage**:

It reflects the level of progression based on degree of fibrosis, ranging from mild portal fibrosis (1) to cirrhosis (6).

LIVER DYSFUNCTION AND RHEUMATOLGY

A. Primary diseases of liver in which joints are involved:

1. Autoimmune hepatitis
2. Acute viral hepatitis
3. Primary Biliary Cirrhosis
4. Hemochromatosis
5. Wilson's disease

B. Primary Rheumatological diseases in which liver is involved:

1. Rheumatoid arthritis/ Sjogren's syndrome
2. Felty's syndrome
3. Juvenile idiopathic arthritis (JIA)
4. Adult onset Still's disease (AOSD)
5. Systemic lupus erythematosus
6. Systemic sclerosis
7. Polymyalgia rheumatica
8. Polyarteritis nodosa

C. Antirheumatic drug induced liver disease

Primary diseases of liver with Rheumatological involvement:

- **Primary Biliary Cirrhosis (PBC)**[16-18]

  5 – 9.7 % of patients with PBC have Rheumatoid arthritis. 64 % have positive Rheumatoid factor of which majority show asymptomatic joint erosions. Symptomatic arthritis is seen in 10% of patients. The sicca complex of dry eyes and mouth is seen in 72%. Scleroderma and CREST syndrome are in 17 %, whereas Raynaud's phenomenon is seen in 12% of patients. Flitting arthritis is seen in this disease and is due to hypercholesterolemia. Digital clubbing and hypertrophic osteoarthropathy have been reported to occur in 35-38% of patients. [19]

- **Autoimmune hepatitis**

  It is commonly associated with arthralgia, stiffness in large joints. Rheumatoid factor and ANA are positive in 95% and 84% of patients respectively [19]. Joint swelling and effusion are less common features.

- **Viral hepatitis**

  Serum sickness like illness, arthralgia, and rash are seen transiently especially in acute viral hepatitis caused by Hepatitis B virus.

  Non erosive arthritis and other manifestations are most likely due to an immune complex mediated disorder.

- **Hemochromatosis/ Wilson's**

  Chronic arthropathy may be the only presenting symptom [20]. 75% of patients with Wilson's disease have signs and symptoms related to locomotor system in the form of pain and stiffness of knees and spine. Hyperextensible joints in the absence of Marfan's syndrome or homocysteinuria is another characteristic feature.

Rheumatic diseases with liver involvement

- **Rheumatoid arthritis (RA) / Sjogren's syndrome** [21]

  Hepatomegaly is seen in 10% of RA and 15% of Sjogren's but other clinical signs of chronic liver disease are uncommon. Abnormal biochemistry in the form of elevated liver enzymes, low serum albumin and elevated globulin are frequently seen. Antimitochondrial antibodies are seen in < 1% of RA, 1.5% of Sjogren's and 6% of patients with Sicca syndrome. Liver biopsy shows non specific hepatitis in 43% and fatty change in 22% of patients.

- **Felty's syndrome** [22]

  It is mentioned separately due to frequent association with nodular regenerative hyperplasia of liver, portal hypertension and its complications. Abnormal biochemistry is seen in > 60% of patients

and liver biopsy shows Kupffer cell prominence and sinusoidal lymphocytic infiltration.

- **Juvenile Idiopathic Arthritis (JIA)** [22]

  Hepatic dysfunction is common with systemic onset disease. Elevated Bilirubin and liver enzymes are seen in a fifth of all cases with liver biopsy showing periportal lyphocytic infiltration and Kupffer cell hyperplasia.

- **Adult onset Still's disease (AOSD)** [23]

  30% of patients have liver involvement in the form of mild hepatomegaly. Modest elevation of liver enzymes with similar histological features of periportal infiltration is common. Rare occurrence of acute liver failure is life threatening complication of AOSD.

- **Systemic lupus erythematosus (SLE)**

  Hepatomegaly is seen in 23-39% of patients with lupus. Elevated transaminases and jaundice is seen in 24% of cases. Cirrhosis and complications are seen in 2% of patients whereas abnormal liver histology is seen with 21% of cases. 20% of chronic autoimmune hepatitis patients have positive criteria for SLE. [31]

- **Antirheumatic drug induced liver disease**

  Hepatotoxicity is a rare, unpredictable, and dose independent complication of drugs used to treat rheumatological diseases. Aspirin causes elevated transaminases and in high doses can cause Reye's syndrome in children. Indomethacin and Ibuprofen are relatively safe with isolated reports of fatty change and hepatitis. Toxic granulomatous hepatitis is a life threatening complication of Phenylbutazone occurring in 0.25% of patients. Gold hepatitis with intrahepatic cholestasis has been well documented. Penicillamine and Azathioprine are known to cause transaminase elevation and cholestasis. Methotrexate causes hepatic fibrosis after a cumulative dose.

Autoimmune Hepatitis

Autoimmune hepatitis is a nonresolving inflammation of the liver of unknown cause. It is characterized by the presence of interface hepatitis on histological examination, hypergammaglobulinemia, and autoantibodies. There are no features that are absolutely diagnostic, and the existence of the condition can be established only by recognition of a constellation of compatible features and the exclusion of other diseases. [24]

The *sine qua non* of the diagnosis is the presence of interface hepatitis in liver biopsy tissue. Plasma cell infiltration strengthens the histological diagnosis, but it can occur in other forms of acute and chronic liver disease. The absence of plasma cell infiltration does not preclude the diagnosis. Other histological features include panacinar (lobular) hepatitis and centrilobular necrosis. [25]

Occurrence

The incidence of autoimmune hepatitis among white northern Europeans is 1.9 cases per 100,000 persons per year, and its point prevalence is 16.9 cases per 100,000 persons per year. [26] In India incidence is said to be less than 1 case per 100,000 persons per year. [27]

The disease occurs as commonly across all age ranges, and it is under-diagnosed in the elderly. It is also a diagnosis that can and should be made in infants. Seventy-eight percent of patients are women, and the female: male ratio is 3.5. Women with autoimmune hepatitis have higher frequencies of concurrent immune diseases than men with the disease.

Symptoms and Clinical Features

Fatigue and myalgia are the most common symptoms, but 34% of patients are asymptomatic at presentation. These patients are typically discovered during routine general medical examinations that include the screening of

liver tests. Asymptomatic patients are more commonly men, and they have lower serum levels of aminotransferases and globulins at presentation than symptomatic patients. Histological features are similar between symptomatic and asymptomatic patients, and there is no significant difference in the occurrence of cirrhosis. Seventy percent of asymptomatic patients become symptomatic, and the absence of symptoms at presentation should not deter treatment. [25]

An abrupt, rarely fulminant, presentation is possible, and the diagnosis does not require 6 months of continuous activity to establish its chronicity and nature. Hepatomegaly is the most common physical finding, but 25% of patients will have normal physical examinations.

Concurrent immune diseases, including autoimmune thyroiditis, ulcerative colitis, and Graves' disease, occur in 38% of patients, and celiac disease is important to recognize because it is typically asymptomatic, and it may contribute to the liver dysfunction. Immune diseases may develop at any time during the course of autoimmune hepatitis. [24]

Laboratory Features

The predominant abnormalities are elevated serum aminotransferase levels, which can mimic a severe acute hepatitis. Most patients have substantial increases in the serum gamma-globulin and immunoglobulin G levels.

Strong cholestatic features, mainly serum alkaline phosphatase levels that exceed 2-fold the upper limit of normal, discourage the diagnosis. Only 21% of patients have serum alkaline phosphatase levels that exceed 2-fold normal, and none with classical disease have serum alkaline phosphatase levels that exceed 4-fold normal. A disproportionately increased serum alkaline phosphatase level points to an alternative diagnosis. [25]

Conventional Serologic Markers

Smooth muscle antibodies (SMA), antinuclear antibodies (ANA), and antibodies to liver kidney microsome type 1 (anti-LKM1) constitute the serologic markers for autoimmune hepatitis. None of the autoantibodies is pathogenic for the disease or diagnostic of the condition; their presence supports the need for further diagnostic testing. SMA and ANA are the most common serologic manifestations of autoimmune hepatitis, and each may appear and disappear in varying titer independently. High titers (titers ≥ 1:160) support the immune nature of the liver disease, but low titers (titers 1:40-1:80) do not preclude the diagnosis in patients with other compatible features. [25]

Liver biopsy assessment is essential to evaluate the nature of the disease regardless of the serologic profile. Patients with interface hepatitis who lack the conventional autoantibodies may have "autoantibody-negative

autoimmune hepatitis. These patients may be classified as having definite disease if repeat testing reveals SMA, ANA, or anti-LKM1, or nonstandard autoantibodies such as perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antibodies to soluble liver antigen/liver pancreas (anti-SLA/LP) are detected.

Nonstandard Serologic Markers

Nonstandard autoantibodies are still being evaluated as diagnostic and prognostic indices and have not been formally incorporated into clinical algorithms. Nevertheless, they have the promise of enhancing diagnostic specificity and adding a prognostic dimension to the serologic profile. Perinuclear antineutrophil cytoplasmic antibodies (pANCA) may be useful in classifying patients who lack the conventional serologic markers, and IgA antibodies to EMA may identify individuals with celiac-related liver disease. Antibodies to SLA/LP, actin (antiactin), chromatin (antichromatin), asialoglycoprotein receptor (anti-ASGPR), and liver cytosol type 1 (anti-LC1) have been associated with severe disease or poor treatment response, and some autoantibodies may be reflective of genetic propensities that affect outcome.

Antibodies to SLA/LP and actin have been associated with human leukocyte antigen (HLA) DR3, and there may be other serologic expressions with a similar genetic association that augur a poor prognosis. The major clinical limitation of the nonstandard autoantibodies has been their low individual occurrence in patients with autoimmune hepatitis. The variable and infrequent expression of these antibodies in individuals with autoimmune hepatitis limits the value of any one determination in assessing prognosis, especially because the absence of the prognostic marker does not preclude a poor outcome

Clinical Subtypes

Two types of autoimmune hepatitis have been proposed on the basis of serologic markers. These types have not been established as valid clinical entities, but the terms have been useful as clinical descriptors. **Type1 autoimmune hepatitis** is the most common form worldwide, and it is characterized by the presence of ANA or SMA. Eighty percent of adults with autoimmune hepatitis have this disease type. [32]

Type 2 autoimmune hepatitis is characterized by the presence of anti-LKM1 antibodies and occurs mainly in children and in Europe. Twenty

percent of patients with type 2 autoimmune hepatitis in Europe are adults. The disease subgroups have not been associated with a distinctive prognosis or treatment strategy. The major clinical value of this stratification has been to describe certain clinical phenotypes, and the major investigative value has been to identify homogeneous populations in which to evaluate pathogenic mechanisms. [28]

Table 1.1 Subtypes of Autoimmune Hepatitis

Clinical Features	**Type 1**	**Type 2**
Signature autoantibodies	SMA/ ANA	LKM1
Ancillary autoantibodies	pANCA/ Antiactin	LC1
Autoantigen	Unknown	CYP2D6
Age (years)	Infancy to old age	Pediatric (2-14)
Women (%)	78	89
Immune diseases (%)	38	34
Typical concurrent immune diseases	Thyroiditis Graves' disease Ulcerative colitis	Thyroiditis Vitiligo Type 1 diabetes
HLA associations	B8, DR3, DR4	B14, DR3, C4A-Q0, DR7
Allelic risk factors	*DRB1*0301* *DRB1*0401*	*DRB1*07*
Steroid responsive	+++	++

Variant syndromes [29]

Patients with features of AIH and another liver disease ("overlap syndromes") or with findings that are inconsistent with the definite diagnosis of AIH ("outlier syndromes") constitute the variant syndromes. These variant forms have been reported extensively but the overall experience with these conditions remains relatively small and anecdotal. Standardised diagnostic criteria have not been promulgated; experiences between institutions have not been compared; natural history for each variant form remains uncertain; and treatment algorithms have not been validated. Eighteen per cent of patients with autoimmune liver disease have features that vary from the classical syndromes of AIH, primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC), and patients with PSC most commonly have concurrent features of AIH that confound the diagnosis. Recognition of these variants is important because they are common; their inclusion in classical diagnostic categories can distort perceptions of disease behaviour and outcome; responsiveness to conventional therapies may vary; and they may provide clues to the pathogenesis of the typical disorders.

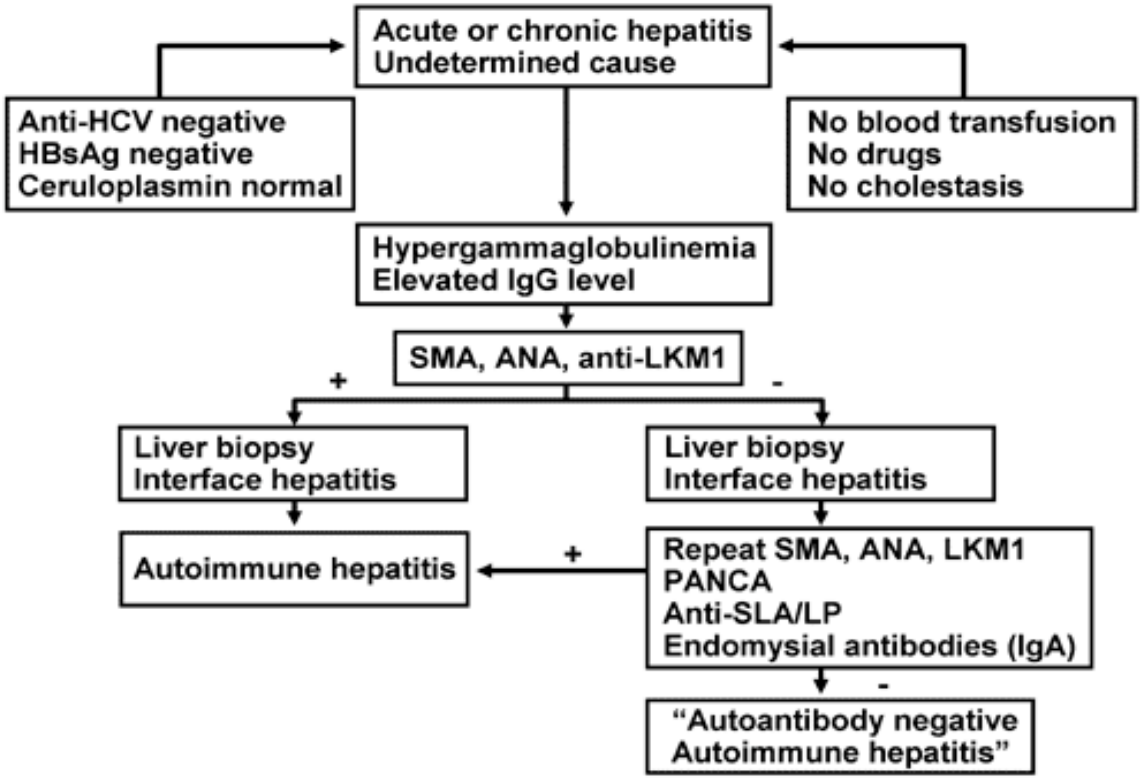
SLE and Autoimmune liver disease [46]

Although the liver is not a major target for damage in SLE, clinical and biochemical evidence of liver abnormalities are common. However, abnormality of liver function is not a diagnostic criterion of SLE. After careful exclusion of various etiologies of liver disease, the question remains as to whether to classify the patient as having a primary liver disease with associated autoimmune features or having liver disease as a manifestation of SLE. Whether AIH and SLE-associated hepatitis are two distinct entities remains unclear. Several clinical and histological features have been used to discriminate AIH from SLE, since complications and therapy are very different in the two conditions.

Patients with SLE have a 25%-50% chance of developing abnormal liver tests in their lifetime. The frequency of liver dysfunction and the associated portal inflammation support the view that subclinical liver disease is a concomitant feature of SLE. Histologically, the most common findings are fatty infiltration, and atrophy and necrosis of the central hepatic cells.

Approach to Diagnosis

The diagnosis of autoimmune hepatitis has been codified by an international panel, and these criteria must now be applied to all patients suspected to have the disease. The *definite* diagnosis requires the exclusion of other similar diseases; laboratory findings that indicate substantial immune reactivity; and histologic findings of interface hepatitis. A cholestatic form of autoimmune hepatitis is unrecognized, and patients with pruritus, hyperpigmentation, xanthelasmas, or disproportionately elevated serum alkaline phosphatase levels must be evaluated for other conditions. A *probable* diagnosis is justified when findings are compatible with autoimmune hepatitis but insufficient for a definite diagnosis. Patients who lack conventional autoantibodies but who are seropositive for investigational markers, such as antibodies to SLA/LP, actin, or LC1, are classified as having probable disease. [34]



DIAGNOSTIC ALGORITHM FOR AUTOIMMUNE HEPATITIS [34]

Table 1.2 International Criteria for the Diagnosis of Autoimmune Hepatitis [37]

Diagnostic Criteria	
Definite AIH	**Probable AIH**
Normal alpha-1 AT phenotype Normal ceruloplasmin level Normal iron and ferritin levels	Partial alpha-1 AT deficiency Nondiagnostic ceruloplasmin/copper levels Nondiagnostic iron and/or ferritin changes
No active hepatitis A, B, and/or C infection	No active hepatitis A, B, and/or C infection
Daily alcohol < 25 g/day No recent hepatotoxic drugs	Daily alcohol < 50 g/day No recent hepatotoxic drugs
Predominant serum AST/ALT abnormality	Predominant serum AST/ALT abnormality
Globulin, gamma-globulin or IgG level ≥ 1.5 times upper limit of normal ANA, SMA, or anti-LKM1 ≥ 1:80 in adults and ≥ 1:20 in children; no AMA	Hypergammaglobulinemia of any degree ANA, SMA or anti-LKM1 ≥ 1:40 in adults; other autoantibodies
Interface hepatitis, moderate to severe No biliary lesions, granulomas, or prominent changes suggestive of another disease	Interface hepatitis, moderate to severe No biliary lesions, granulomas, or prominent changes suggestive of another disease

Diagnostic scoring

A scoring system accommodates the diverse manifestations of autoimmune hepatitis and renders an aggregate score that reflects the net strength of the diagnosis before and after corticosteroid treatment. Each component of the syndrome is weighed, discrepant features are discounted, and biases associated with isolated inconsistencies are prevented. The scoring system was developed as a research tool to ensure comparable study populations in clinical trials, and it is not a discriminative diagnostic index. The sensitivity of the scoring system for autoimmune hepatitis ranges from 97% to 100%, and its specificity for excluding chronic hepatitis C ranges from 66% to 92%. The major weaknesses of the scoring system have been its complexity and difficulty in distinguishing autoimmune hepatitis from cholestatic syndromes with autoimmune features (accuracy, 45% to 65%). A streamlined modification of the scoring system has been developed and is now being promulgated. [34, 38]

Table 1.3 International Scoring System for Diagnosis of Autoimmune Hepatitis [34]

Sex	Female	+2		**HLA**	DR3 or DR4	+1
AP:AST (or ALT) ratio	> 3 < 1.5	-2 +2		**Immune disease**	Thyroiditis, colitis, others	+2
Gamma-globulin or IgG level above normal	> 2.0 1.5-2.0 1.0-1.5 < 1.0	+3 +2 +1 0		**Other markers**	Anti-SLA/LP, actin, LC1, pANCA	+2
ANA, SMA, or anti-LKM1 titers	> 1:80 1:80 1:40 < 1:40	+3 +2 +1 0		**Histologic features**	Interface hepatitis Plasmacytic Rosettes None of above Biliary changes Other features	+3 +1 +1 -5 -3 -3
AMA	Positive	-4		**Treatment response**	Complete Relapse	+2 +3
Viral markers	Positive Negative	-3 +3				
Drugs	Yes No	-4 +1		**Pretreatment score** Definite diagnosis: > 15 Probable diagnosis: 10-15		
Alcohol	< 25 g/day > 60 g/day	+2 -2		**Posttreatment score** Definite diagnosis: > 17 Probable diagnosis: 12-17		

Treatment

Corticosteroid therapy is effective in all forms of autoimmune hepatitis, and the combination of prednisone and azathioprine is preferred. Remission can be achieved in 80% of patients within 3 years, and the 10- and 20-year survival rates exceed 80%. Histological cirrhosis does not affect response or longevity, and all patients with severe disease should be treated, including children, elderly adults, postmenopausal women, individuals with acute or fulminant presentations, and those without conventional autoantibodies. Relapse is common, and long term low-dose prednisone or azathioprine therapy is preferred after multiple relapses. Sustained remission is achievable, even after relapse, in 47% within 10 years, and the long-term maintenance regimens need not be indefinite. Liver transplantation is effective, and its actuarial 10-year survival rate is 75%. Drugs such as cyclosporine, tacrolimus, and mycophenolate mofetil promise greater blanket immunosuppression, and site-specific interventions are feasible, including blocking peptides, soluble cytotoxic T lymphocyte antigen-4, cytokine manipulations, T cell vaccination, oral tolerance, and gene therapy. (30, 33, 36)

Table 1.4

Conventional treatment regimen [36]

	Combination Therapy		Prednisone Therapy
Weeks Administered	**Prednisone (mg daily)**	**Azathioprine (mg daily)**	**Prednisone (mg daily)**
1	30	50	60
1	20	50	40
2	15	50	30
Maintenance until endpoint	10	50	20
Optimal Indications			
	Post-menopausal state Osteoporosis or vertebral compression Diabetes Hypertension Obesity Emotional lability/depression	Cytopenia Pregnancy Active malignancy Short course Thiopurine methyltransferase deficiency	

Table1.5
Management Options Using Evolving but Unestablished Drug Therapies [30]

Treatment Status	Evolving Drug Therapies			
Naïve	Cyclosporine (5-6 mg/kg daily)	Budesonide (3 mg twice daily)	Ursodeoxycholic acid (13-15 mg/kg daily)	
Treatment failure	6-mercapto purine (1.5 mg/kg daily)	Mycophenolate mofetil (2 g daily)	Cyclosporine (5-6 mg/kg daily)	Tacrolimus (4 mg twice daily)
Incomplete response	Budesonide (3 mg twice daily)	Ursodeoxycholic acid (13-15 mg/kg daily)		Deflazacort (7.5 mg for every 5 mg prednisone daily)
Drug toxicity	6-mercapto purine (1.5 mg/kg daily)	Cyclosporine (5-6 mg/kg daily)	Mycophenolate mofetil (2 g daily)	Ursodeoxycholic acid (13-15 mg/kg daily)
Relapse	Mycophenolate mofetil (2 g daily)	Deflazacort (7.5 mg for every 5 mg prednisone daily)		

Prognosis and survival

In a large retrospective analysis of patients with AIH, all of whom received immunosuppressive therapy, the overall five-year survival was 85%. Those with cirrhosis had a significantly worse prognosis. Patients who were anti-LKM antibody positive were also reported to have a poorer prognosis but this is probably accounted for by the high frequency of cirrhosis in this group. [41]

Causes of death

Other than incidental, non-hepatic causes, death is now largely a consequence of cirrhosis. In the small group of steroid-resistant cases, and the few who present with fulminating disease, death may be due to acute hepatic failure and its complications—although liver transplantation is increasingly becoming a life-saving option in these cases. For the majority, hepatocellular failure secondary to cirrhosis is the major cause of death, followed by variceal haemorrhage, septic complications,and hepatocellular carcinoma.

Autoimmune Hepatitis – Indian scenario

There is considerable geographic variation in frequency and clinical manifestations of autoimmune hepatitis in our country. This is expected considering the heterogeneity in genetic makeup and environmental influences. It has been regarded as a rare cause of liver disease in India. [27] This may in part be due to non specific nature of symptoms and inability to recognize the disease in the initial phases. It is also due to the lack of awareness about the condition among general physicians and continued use of alternative/ herbal medicines for all patients with liver disease.

The bottom line is that Indian data regarding the incidence, clinical, biochemical and histological profile of autoimmune hepatitis is scarce. Studies from SGPGI Lucknow and Mumbai uniformly reported an incidence of 1.5-2% of all liver disease. [27] Mean age at presentation was 36 yrs with 90% of patients being women. 50% presented with chronic hepatitis, 35% with Cirrhosis and 15% as acute hepatitis. Clinical manifestations were jaundice (55%), edema and hepatomegaly (44%), Splenomegaly (35%), fever (21%) and encephalopathy (24%). Autoimmune markers seen were ASMA (57%), ANA (36%) and both (10%). Anti LKM, ANCA were not seen. [27]

Reasons for the study

From the above review it is clear that liver involvement in autoimmune disease is known to occur. Autoimmune liver disease is a common cause of liver disease among women. It is an emerging condition in our country and due importance has not been given in Indian literature like that given to the commonly reported causes of chronic liver disease in India i.e. alcohol and HBV/ HCV related chronic hepatitis. The available data is scarce and mainly from north and west India with no studies from the south.

Most of the studies in literature, including those from the west, tended to proceed from effect to cause i.e. to look at autoimmune etiology in patients with liver disease. This is a unique study, which addresses the problem from the other angle, by detecting liver involvement in autoimmune disease. This is important, from the point of improving our knowledge about the early natural history of the condition, and also provides the opportunity for recognizing those at risk for chronic liver disease and preventing its progression.

3. AIMS AND OBJECTIVES

- To study the occurrence, clinical presentation, and biochemical/ immunological profile of liver involvement in autoimmune diseases.
- To trace the natural history of autoimmune liver disease before the development of symptomatic liver disease.
- To analyse the possible etiology of liver involvement in autoimmune disorders.
- To formulate locally applicable protocols for diagnosis and treatment of autoimmune hepatitis.

4. MATERIALS AND METHODS

STUDY DESIGN

Prospective cohort study

VENUE OF THE STUDY

Rheumatology clinic, Govt. Stanley hospital, Chennai

STUDY PERIOD

Jan 2007 – May 2007

STUDY POPULATION

All cases of SLE and Rheumatoid arthritis satisfying the criteria.

INCLUSION CRITERIA

- All newly diagnosed cases of SLE and Rheumatoid arthritis by the American Rheumatological Association (ARA) criteria. [39, 40]
- Age > 12 yrs.
- Positive immune serological tests (RF/ ANA).

EXCLUSION CRITERIA

- Significant alcohol intake (> 40 gm/ day).
- Acute febrile illness.
- Positive viral markers (HBsAg/ anti HCV).
- Suspected or proven metabolic liver disease.

METHODS

This study was carried out in the rheumatology clinic of GOVT. STANLEY HOSPITAL, Chennai. This is a tertiary referral center catering to large population in north Chennai and neighboring districts of Thiruvallur, Kanchipuram, and Villupuram. Outpatient attendances at the clinic are about a hundred per day with an equal number of new and follow up cases.

Newly diagnosed cases of SLE and Rheumatoid arthritis were enrolled into the study. Informed consent was taken from all participants. The demographic profile and clinical history was recorded including complaints of liver involvement, connective tissue involvement and associated endocrine involvement. Relevant drug history was sought including alternative and herbal medicines. Detailed physical examination was done on all patients, with special attention paid to looking for features of autoimmune phenomenon, like alopecia, viltigo and signs of liver disease like icterus, edema, hepatosplenomegaly and ascites.

Routine labs included complete blood count and ESR. Tests of liver function were recorded including prothrombin time. Immunological markers Rhematoid factor (RF) and anti-nuclear antibody (ANA) was done by

immunoflourescence method. Imaging included an ultrasound scan of the abdomen. The liver size and echoes, spleen size, portal vein diameter, presence of collaterals and free fluid were recorded. Upper GI endoscopy was done for cases when indicated to look for evidence of portal hypertension.

Data collected in the study proforma was organized and compiled using the Microsoft excel worksheet software version 2006. This was analysed using statistical tools to calculate mean, median and incidence using internet based calculators.

5. RESULTS

A total of 50 subjects satisfying the inclusion criteria were enrolled into the study. The mean age of the subjects was 35yrs, range 12-60 yrs and the median age was 33 yrs. There were 40 female patients compared to 10 male with male to female ratio of 1:4. The mean duration of illness before presentation to our clinic was 5 months; range 1-12 months.

AGE DISTRIBUTION

Of the 50 patients, 8 (16%) belonged to the group of ≤ 20 yrs whereas 15 (30%) were between 21- 30 yrs. The 31- 40 yrs consisted of 9 (18%) patients and another 12 (24%) came in the 41-50 yrs group. The rest, i.e. 6 (12%) belonged to the > 50 yrs group.

Table 1. AGE DISTRIBUTION OF SUBJECTS

AGE (yrs)	SLE	RA	TOTAL
<20	7	1	8
21-30	5	10	15
31-40	0	9	9
41-50	1	11	12
>50	1	5	6

SEX DISTRIBUTION

The overall male to female ratio was 1:4. More specifically among SLE patients the ratio was 1:6, whereas among Rheumatoid arthritis patients it was 2:7.

Table 2. SEX DISTRIBUTION OF SUBJECTS

SEX	SLE	RA
Male	2	8
Female	12	28

PRIMARY ILLNESS

Of the 50 patients enrolled in the study, 14 (28%) were diagnosed to have SLE, whereas 36 (72%) had features of Rheumatoid arthritis.

SYMPTOMATOLOGY AND ANALYSIS

Overall the frequent presentation was with non specific symptoms of arthralgia, myalgia and loss of apetitie. Most of the patients presented as a chronic fatigue syndrome. Thirty patients (60%) reported to have fatigue, 44 (88%) had arthralgia and 41 (82%) had myalgia. Jaundice, GI bleed were less frequent.

Table 3. INCIDENCE OF SYMPTOMS

Symptoms	Incidence
Fatigue	60% (30/50)
Anorexia	28% (14/50)
Myalgia	82% (41/50)
Arthralgia	88% (44/50)
Jaundice	12% (6/50)
GI bleed	8% (4/50)

Myalgia, fatigue and anorexia were more common with SLE than Rheumatoid arthritis. GI bleed and jaundice occurred only in SLE patients.

Table 4. DISTRIBUTION OF SYMPTOMS

Symptoms	SLE	RA
Fatigue	100%	44%
Anorexia	92%	2%
Myalgia	92%	78%
Arthralgia	78%	91%
Jaundice	43%	0%
GI bleed	28%	0%

ASSOCIATED DISEASES

Diabetes was the common associated disease, seen in 30% (15/50) of cases, whereas thyroid disorders were seen in 18% (9/50) patients. Both were more frequent in Rheumatoid arthritis patients.

Table 5. INCIDENCE OF ASSOCIATED DISEASES

Associated disease	SLE	RA
Diabetes	1/14 (7%)	14/36 (39%)
Thyroiditis	1/14 (7%)	8/36 (22%)

DRUGS

Two- thirds of the patients gave history of drug intake in recent past (33/50). NSAIDs were the commonly used seen in 23 cases (46%). A fifth (10) of the patients reported to using drugs of Indian systems of medicine (Ayurveda/ Homeopathy/ Siddha).

CLINICAL SIGNS

There was a paucity of clinical signs of liver disease like spider nevi, dilated veins, flapping tremors etc. Common features were edema, arthritis, and alopecia. Hepatomegaly was seen in 38% (19) of the cases. Other signs of liver disease like jaundice, Splenomegaly and ascites were infrequent and seen mostly in SLE patients. Three patients with SLE (21%) had physical findings of decompensated chronic liver disease and portal hypertension.

Table 6. INCIDENCE AND DISTRIBUTION OF PHYSICAL SIGNS

PHYSICAL SIGNS	SLE	RA
Icterus	6/14 (44%)	0
Edema	11/14 (78%)	10/36 (27%)
Arthritis	7/14 (50%)	31/36 (87%)
Hepatomegaly	9/14 (64%)	10/36 (28%)
Splenomegaly	3/14 (21%)	0
Ascites	5/14 (36%)	0

INVESTIGATIONS

Anemia and elevated acute phase reactants like sedimentation rate and C-reactive protein was frequently seen. Mean Hb was 9.6 gm% whereas mean ESR was 66 mm at 1 hr.

Modestly elevated bilirubin upto 5 mg% was seen in 6 patients (12%), of which 3 had decompensated liver disease. Mean albumin was 3 gm/ dL, and low albumin (< 2.5g %) was seen in 8 cases (16%). Mean Globulin level was 3.1 gm/dL; Elevated globulin (> 3.4 gm %) was seen in 21 cases (42%).

Elevation of Liver transaminases was defined as level > 2 upper limit of normal (35 iU/L) [42]. Alanine aminotransferase (ALT) was elevated in 29 (58%) cases. Elevation in alkaline phosphatase (ALP) was modest.

Table 7. INCIDENCE OF LIVER ENZYME ELEVATION

DIAGNOSIS	ALT	AST
SLE	12/14 (86%)	9/14 (64%)
RA	17/36 (48%)	11/36 (30%)

Immunological markers, Antinuclear antibodies (ANA) was positive in 19 (38%) cases and Rheumatoid factor (RF) in 40 (80%) patients. Both were positive in 5 (10%) patients.

Table 8. INCIDENCE OF SEROLOGICAL MARKERS

SEROLOGY	INCIDENCE
ANA	38%
RF	80%

ULTRASOUND FINDINGS

Hepatomegaly was most frequent finding overall. Fatty liver was seen in 9 (18%) patients. Three cases with decompensated liver disease had dilated portal vein diameter (> 1.3 cm) and Splenomegaly. Ascites was present in 8 (16%) of scans.

Table 9. ULTRASOUND FINDINGS

ULTRASOUND FINDING	INCIDENCE
Hepatomegaly	12/50 (24%)
Shrunken Liver	2/50 (4%)
Fatty Liver	9/50 (18%)
Coarse Echoes	3/50 (6%)
Splenomegaly	3/50 (6%)
Dilated Portal vein	3/50 (6%)
Ascites	8/50 (16%)

All the sonogram findings were more common in SLE than Rheumatoid arthritis. Splenomegaly, ascites and dilated portal vein were exclusively seen in SLE. Two cases of SLE had shrunken liver and three had coarse echoes.

Table 10. DISTRIBUTION OF ULTRASOUND FINDINGS

ULTRASOUND FINDINGS	SLE	RA
Hepatomegaly	9/14 (64%)	3/36 (8%)
Shrunken Liver	2/14 (14%)	0
Fatty Liver	4/14 (28%)	5/36 (14%)
Coarse Echoes	3/14 (21%)	0
Splenomegaly	3/14 (21%)	0
Dilated Portal vein	3/14 (21%)	0
Ascites	8/14 (57%)	0

ENDOSCOPY

Esophageal varices were seen on upper GI endoscopy in 3 patients (7%).

All these cases belonged to the SLE group and were diagnosed to have decompensated chronic liver disease with portal hypertension. One patient in the SLE group underwent colonoscopy for hematochezia which revealed findings consistent with Ulcerative colitis.

6. DISCUSSION

The findings of this study corroborate well with national and international literature but at the same time highlight some interesting points of difference between the two. This may be attributed to the genetic, geographical and racial differences between our population and the west. Because of the unique perspective of this study, we are able to look at the problem of autoimmune liver disease at its early stage. It provides an opportunity to appreciate the natural history and wide variety of liver manifestations in autoimmune diseases.

A similar account was published by Angela Hilton and others [21], from Univ. Hospital of South Manchester, in the Annals of rheumatic Diseases. This particular study looked at liver abnormalities patients with joint symptoms of varied etiology. Thirty patients suffering from SLE, Rheumatoid arthritis, Gout and other disorders were evaluated with routine liver function tests, immunology and histology. They did not exclude any patients with alcoholic or viral hepatitis.

The commonest abnormality was elevated transaminase (ALT); seen in 19 patients (63%), low serum albumin in 6 patients (20%) and elevated serum globulin in 16 cases (53%). This is comparable to the results of our study, where 29 patients (58%) had elevated ALT, 8 (16%) had low albumin

and 21 patients (42%) had elevated serum globulins. The Manchester study concluded that detailed hepatic investigations are justified in patients with rheumatic diseases, who have hepatomegaly and/or abnormal LFT. Further, it should not be assumed that these abnormalities are due to liver involvement as part of a multisystem autoimmune disease. Specific liver disease must be looked for and treated accordingly when indicated.

Similar results were reported in the study done by Cockel R and Kendall M J [(42)] which was also published in the Annals of Rheumatic Diseases.

An interesting study was done was Koichi Kushimoto and colleagues from Kyushu University in Japan [(43)]. They looked at liver abnormalities in 57 patients with SLE. Elevated transaminases were seen in 56% of cases. Of great interest to us is the finding that three of their patients had fatty liver compared to the four of our SLE patients who also had fatty liver. This gives the impression that autoimmune liver disease probably passes through a phase of fatty liver, similar to that seen in alcoholics, before causing Cirrhosis. The importance of this finding lies in the fact that these individuals can be identified as to being at high risk for development of Cirrhosis, hence requiring aggressive therapy and surveillance.

Rothfield [43] and Morito [44] observed similar abnormalities in SLE patients.

Dubois and Tuffanelli [45] found jaundice in only 3.8% of 520 cases of SLE. Koffman [46] in a study reported jaundice in 12% of SLE patients. This is concurrent to the low incidence of jaundice (6 cases/ 12%) in our study.

Choudhuri et al published a series of 41 cases of autoimmune liver disease [27].This formed 1.7% of all liver disease seen at SGPGIMS Lucknow between 1999 and 2002. The presentations were Jaundice in 21 (55%), fatigue, edema and hepatomegaly in 17 cases (44%), Splenomegaly in 13 cases (34%). Diabetes and thyroiditis were the most common associated extra hepatic diseases. High ESR was seen in 55%, elevated ALT in 75%, and high globulin in 58% of cases. In our study edema was seen in 42%, fatigue in 60% and hepatomegaly in 38% of cases. Lower incidence of Splenomegaly (6%) and jaundice (12%) can be attributed to seeing the patients at an earlier stage before they develop serious liver disease.

There are some shortcomings of our study; mostly due to lack of facilities in the Govt. setup. The obvious one is that liver biopsy was not done for finding the cause for liver dysfunction in these patients. This was technically not feasible in this institution. The other drawback is the non availability of some autoimmune markers like anti smooth muscle antibody (ASMA), anti actin antibody and pANCA titres. A valid criticism was that the design did not include any control population. This was because of the pilot nature of the study and future studies can improve on study design by including larger sample and adequate controls. A hospital based study like this suffers from a referral bias, but this is unavoidable and in any case large population studies for rare diseases are neither feasible nor necessary.

7. CONCLUSION

- Liver dysfunction is common in autoimmune diseases like SLE and Rheumatoid arthritis.
- There is a female predominance; majority of cases are young women.
- Presentations are commonly non specific with myalgia, arthralgia and chronic fatigue syndrome. Symptoms of liver disease are uncommon.
- Diabetes and thyroid disorders are commonly associated disorders.
- Drugs like Nsaids and native medicines may contribute to liver dysfunction in some patients, the nature of which needs to be studied.
- Hepatomegaly and edema are frequent early physical findings; signs of liver disease like Splenomegaly and ascites appear late.
- Transaminase elevation are early and sometimes the only sign of liver involvement. Low albumin and high globulin may be seen in patients.
- Serological markers of autoimmunity are positive in most of the cases. Presence of multiple markers is probably proportional to activity.
- Fatty liver is seen in few cases which may predict the appearance of progressive liver disease at a later stage.
- A small minority of patients present with decompensated liver disease and signs of portal hypertension, with varices and ascites.

This study was undertaken to get an idea about the early natural history of liver involvement in autoimmune disease. The findings suggest that liver involvement is quite common in autoimmune disease. Initially it may be non specific with elevation of transaminases as the sole presentation. Long standing illness may present as decompensated chronic liver disease. It is probable that fatty infiltration of liver may be the missing link of this natural history. Findings which support this are the frequent occurrence of fatty liver in autoimmune diseases like SLE, and also in Hepatitis C related chronic hepatitis which is associated with autoimmune features.

This study also emphasizes a couple of points in the diagnostic aspects of autoimmune liver disease. One is the need for liver biopsy to confirm the diagnosis of autoimmune liver disease. Unfortunately in developing countries this facility is not available at all centers. Secondly, we need to draw our own algorithms and protocols for diagnosing autoimmune liver disease. An ideal protocol will be one which doesn't require a biopsy for diagnosing and starting treatment.

Hence this study provides the platform for further controlled studies with larger sample size using more serological markers. This will help in arriving at our own protocols for diagnosis and treatment.

KEY TO MASTER CHART

- SLE – Systemic Lupus erythematosus
- RA – Rheumatoid arthritis
- F – Female
- M – Male
- P – Present
- A – Absent
- E – Enlarged
- N – Normal
- S – Shrunken
- C – Coarse
- F – Fatty
- V – Varices
- D – Dilated
- IBD – Inflammatory bowel disease
- T. Bili – Total bilirubin
- AST – Aspartate aminotransferase
- ALT – Alanine aminotransferase

- ALP – Alkaline phosphatase

STUDY PROFORMA

Demographic profile

Name: Age/ sex:

Address: Ref no:

Diagnosis

Clinical information

Fatigue: Anorexia: Myalgia:

Jaundice: GI bleed: Thyroid: IBD:

Medications:

Examination

Oral ulcers: Icterus: Edema: Vitiligo:

Goiter: Arthritis: Rash: Alopecia:

Spider nevi: Cushing's: Dilated veins: Hepatomegaly:

Splenomegaly: Ascites:

Liver function tests

T. Bili D. Bili T. Prot Alb Glob

A:G = AST: ALT: SAP: Pro time:

Hemogram

Hb: TC: DC: ESR:

Serology

ANA: RA factor:

Viral markers

HBsAg: Anti HCV:

Ultrasound

Liver size: Echotexture: Spleen:

Portal vein: Free fluid:

Endoscopy

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ETHICAL COMMITTEE APPROVAL

Ref.No. /ME1/2007

Stanley Medical College,
Chennai-1 Dt. -9-2007

Sub:Medical Education – Stanley Medical College, Chennai – Ethical Committee constituted for approval of Dissertation/ Thesis submitted – regarding.

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The Ethical Committee meeting was held on 3-9-2007 and 7-9-2007 to discuss the paper submitted for Dissertation /Thesis.

The following Members of the Ethical Committee were present and discuss in detail for the approval of the papers presented by the individual by means of power point presentation.

Dr.A.Sundaram, Dean incharge,
Dr.S.Madhavan, Prof. of Pharmacology,
Dr.Thenmozhivalli, Prof. of Microbiology,
Dr.S.Natarajan, Prof. of Medicine,
Dr.K.Balasubramanian, Prof. of Physiology,
Dr.M.L.Shyamala, Prof. of Surgery,
Thiru M.Panneerselvam, Junior Administrative Officer.

LIST OF PAPERS SUBMITTED FOR ETHICAL COMMITTEE APPROVAL
ETHICAL MEETING

Dr. Kiruba Mohan, Prof. of Dermatology

1."N.O.C. for PMS study of pregabalin" - Dr.Parimalam Kumar
2. " A Phase IIb/III trial of LLL-3348 of lupin ltd in plaque psoriasis - Dr.A.Ramesh

Dr.M.Thirunavkarasu, M.D.(Psy)D.PM , Prof. of Psychiatry

"Prevalence, socio-demographic variables and method of suicide among various causes of death."

(2)Psychological autopsy of suicide.

V.Rohit
Effect of chewing gums (XYLITOL)

K.Chinthnidhi
Mycotic infections in immuno compromised and cancer patients.

Malavika Prasad
Profile of Hypertensive emergencies - A study of 100 cases from Dept. of medicine, GSH.
~~~~~~~~~~

3. Sandhya Rani.C Final MBBS,

Assessment of coverage and quality of maternal and child health servic at Minjur Primary Health Centre; Block level

4.C.Muralidharan, Final year.

The implications of mobile phones on hearing loss.

5.V.Sarath Chander, 3rd MBBS

Prevalence of Deafness in children.

6.B.Madhusoothanan, 3rd year

(1) Lung functions in type 2 diabetes.

(2)Hyponatremia in intensive medical care patients in GSH.

7.S.Sathyapriya - II MBBS.,

"A study about screening tests for cases of urinary tract infections (UTIs)Using Urine samples."

8.S.Moogaambiga,

"Estended spectrum beta lactamase producing microbes.

POST GRADUATES

1.Dr.R.Arunprakas -M1. P.G.

Analysis of clinical profile of systemic lupus erythematosus

2.Dr.S.Murugananth - M.2 P.G.

Clinical Profile of infectious fevers

3.Dr.N.Loganathan - M2 P.G.

Clinical and Epidemiological profile of Human Leptospirosis in North Chennai.

4.Dr. K. Babu - M3 - P.G.

Study of Clinical Profile of patients with acute inferior wall myocardial infarction.

5.Dr. S.P.Maharajan - M3 - P.G.

Analytical study of atrial fibrillation in Govt. Stanley Medical College Hospital.

6.Dr.P.R.Sowmini - M3 - P.G.

Clinical profile of arrhythmias complicating acute anterior wall myocardial infarction.

7.Dr.E.Uma Maheswari - M4 - PG

Clinical Radiological analysis of Focal seizures with CT Scan.

8.Dr.S.Sudha Selvi, M4 - PG

Clinical profile of chronic obstructive pulmonary disease.

9.Dr.N.Jayanthi. M6- PG

Prevalence of B2 glycoprotein 1 Dependent anticardiolipin antibodies in acut ischemic stroke.

10.Dr.Lavanya. S. - MD PG

Comparative study of fasting lipid profile in chronic renal failure patients on conservative management, on dialysis and after renal transplant.

11.Dr.R.Geetha - Pharmacology

Evaluation of the sedative effects produced by antihistamines inhealthy volunteers by new techniques.

12.Dr.K.G.Devibala, Pharmacology

To evaluate the efficacy of rupatadine in controlling pruritis in lichen planus.

13.Dr.B.Anitha, Physiology

Visual Evoked potentials in hypothyroid patients.

14.Dr.M.Thirumaran, Physiology

Heart rate variability analysis in alcohol dependant individuals.

15.Dr.K.Vinod, Anaesthesia

Real time ultra sound guided catheterization of IJV – A prospective comparison with land mark guided technique.

16.Dr.Rajesh. C.P. – M6 – PG

Cardiac conduction abnormalities and asymptomatic myocardial infarction in NIDDM patients.

The papers presented to the Committee members by the Profs./Asst. Prof./Post Graduates/Under graduates were discussed across the table while their presentation.

The above papers discussed in detail with its supportive documents submitted by them and approved the above papers submitted for Ethical Committee.

Name of the Members	Signature
Dr.A.Sundaram, Dean incharge,	
Dr.S.Madhavan, Prof. of Pharmacology,	8/10/07.
Dr.Thenmozhivalli, Prof. of Microbiology,	
Dr.S.Natarajan, Prof. of Medicine,	9.10.2007.
Dr.K.Balasubramanian, Prof. of Physiology,	
Dr.M.L.Shyamala, Prof. of Surgery,	08/10/07.
Thiru M.Panneerselvam, Junior Administrative Officer.	